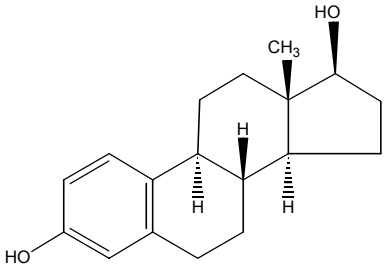
ESTROGENS (NOT CONJUGATED)

ESTRADIOL-17β
CAS No. 50-28-2
First Listed in the *Fourth Annual Report on Carcinogens*



CARCINOGENICITY

Estradiol-17β is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity in experimental animals (IARC V.6 1974; IARC V.21, 1979; IARC S.4, 1982; IARC S.7, 1987). When administered orally, the compound induced increased incidences of adenocarcinomas of the mammary gland, cervix, and uterus, adenoacanthoma of the uterus, and osteosarcoma of the cranium in female mice. Subcutaneous or intramuscular injection induced increased incidences of lymphosarcomas in mice of both sexes. Subcutaneous implants of estradiol-17β induced mammary tumors, including adenocarcinomas, papillary carcinomas, and anaplastic carcinomas in adult and newborn male and female mice and in female rats; pituitary chromophobe adenomas in male rats; fibromyomas of the uterus, mesentery, and abdomen in female guinea pigs; and malignant renal tumors in hamsters of both sexes (IARC V.6, 1974; IARC V.21, 1979).

There is inadequate evidence for the carcinogenicity of estradiol-17β in humans (IARC S.4, 1982). There is sufficient evidence for the carcinogenicity of steroidal estrogens in humans (IARC S.7, 1987). Studies of humans given estradiol-17β alone are not available to IARC Working Groups (IARC V.6, 1974; IARC V.21, 1979; IARC S.4, 1982). However, studies strongly suggest that administration of estrogens is associated with an increased incidence of endometrial carcinoma in humans, and there is no evidence that estradiol-17β is different from other estrogens in this respect. An IARC Working Group concluded that in the absence of adequate data on humans, it is reasonable to regard estradiol-17β as if it presented a carcinogenic risk to humans (IARC V.21, 1979).

PROPERTIES

Estradiol-17β occurs as white or creamy-white prisms at room temperature. It is practically insoluble in water and soluble in ethanol, acetone, chloroform, diethyl ether, dioxane, and solutions of alkaline hydroxides. It is sparingly soluble in fixed oils. Estradiol-17β is unstable in light and air. The compound is available in the United States as a grade containing 97%-103% active ingredient on a dried basis. When heated to decomposition, it emits acrid smoke and fumes.

USE

Estradiol-17β is the most active naturally occurring estrogenic hormone. It is secreted by the ovaries in normal cycling adult females and by the placenta in pregnant females. It is essential for the growth and normal maintenance of the uterine lining, for the development of the accessory and secondary female sex characters, and for support of pregnancy (Prosser, 1973). It is used in human medicine for the treatment of symptoms of the climacteric, particularly for vasomotor and psychological disturbances (IARC V.21, 1979). It is also used for local treatment of atrophic vaginitis, for the chemotherapy of advanced prostatic carcinoma, and for the prevention of postpartum breast engorgement. Estradiol-17β is also used in the treatment of primary amenorrhea, delayed onset of puberty, and chemotherapy of breast neoplasms in postmenopausal women. It is believed to be a component of hormones derived from pregnant mares' urine used in cosmetic skin preparations. Estradiol-17β is used in veterinary medicine for estrogenic hormone therapy, as well as in food-producing animals as a growth promoter (IARC V.21, 1979).

PRODUCTION

Estradiol-17β is a naturally occurring steroid hormone produced endogenously by all mammalian species. The production rate in humans ranges between 6 μg/24 hr in prepubescent boys and 945 μg/24 hr in normal adult cycling females. The 1998 Chemical Buyers Directory lists two U.S. suppliers of estradiol, and Chemcyclopedia 98 names three suppliers (Tilton, 1997; Rodnan, 1997). In 1983, U.S. imports of estradiol-17β totaled 44 lb (USITCa, 1984). U.S. firms also imported 156 lb of the 3-benzoate form in 1983, compared to 379 lb in 1976 and 6 lb in 1975 (IARC V.21, 1979). Commercial production of estradiol-17β in the United States was first reported in 1939 by the U.S. Tariff Commission (IARC S.4, 1982).

EXPOSURE

The primary routes of potential human exposure to estradiol-17β are ingestion, injection, inhalation, and dermal contact. Humans are potentially exposed to exogenous amounts of estradiol-17β through the consumption of meat from treated livestock. However, this is an insignificant amount (2.4 ng/157 g of meat) when compared to normal human production of the chemical. FDA reported that estradiol-17β also is ingested in minute levels through the consumption of milk from untreated dairy cows (about 18 ng in one pint of milk). It has also been found in certain drinking water samples at levels of 0.12-0.42 ng/L. When used as a medication, estradiol-17β is given in doses of up to 1.5 mg two or three times weekly by intramuscular injection, or daily by mouth. Currently, other estrogenic hormones are preferred for oral administration (IARC V.21, 1979). There is some potential for occupational exposure to estradiol-17β through dermal contact and inhalation, for workers involved in the formulation, manufacture, packaging, and administration of pharmaceuticals containing it. The National Occupational Hazard Survey, conducted by NIOSH from 1972 to 1974, estimated that 2,770 workers were potentially exposed to estradiol-17β in the workplace in 1970 (NIOSH, 1976).

REGULATIONS

Because estradiol-17β is used as a pharmaceutical and in low quantities relative to other chemicals, it is not regulated by EPA. However, there may be a small pollution problem relative to hospital wastes. FDA regulates estradiol-17β esters for use as implants in cattle, lambs, and chickens. Estradiol-17β is regulated as a prescription drug for human use under the Food, Drug, and Cosmetic Act (FD&CA). FDA has ruled that estrogens for general use must carry patient and physician warning labels concerning use, risks, and contraindications. OSHA also regulates estradiol-17β under the Hazard Communication Standard and as a chemical hazard in laboratories. Regulations are summarized in Volume II, Table B-59.